[CANCER RESEARCH 48, 3849–3852, July 1, 1988]

Effects of Timing and Type of Tobacco in Cigarette-induced Bladder Cancer[1]

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ABSTRACT

We analyzed a case-control study of bladder cancer in Torino (512 male and 55 female cases; 596 male and 202 female controls) with emphasis on the timing of cigarette smoking and the use of black or blond tobacco. The risk of bladder cancer was 2 to 3 times higher among smokers of black tobacco than among smokers of blond tobacco. Both groups of smokers showed a beneficial effect of smoking cessation, with an immediate decline in risk. This pattern is consistent with a late-stage effect of smoking. Among smokers of black tobacco, there was a gradient of risk with early exposure, and smokers who had quit never showed a drop to base-line levels of risk. These patterns, not apparent in users of blond tobacco, suggest an early stage effect of black tobacco, perhaps due to the higher concentration of aromatic amines in black than blond tobacco smoke and the higher blood levels of the hemoglobin adduct with 4-aminobiphenyl (a human bladder carcinogen) among smokers of black tobacco.

INTRODUCTION

Although cigarette smoking clearly has been shown to increase the risk of developing bladder cancer, the responsible agents and their key stages of action are unknown. We have tried to infer which mechanisms of carcinogenesis may be operating by examining variation in risk according to both the timing of exposure and type of tobacco (black *versus* blond).

The possibility of inferring mechanisms of carcinogenesis from temporal aspects of risk has been explored by several researchers (1–4). Timing of cigarette smoking has been studied in relation to the onset of lung cancer, with evidence suggesting that tobacco smoke contains both early and late stage carcinogens (3, 4). A review on the possible stages at which different exposures, including asbestos, arsenic, and nickel, act on lung cancer risk is available (5). [Experimental evidence also indicates that carcinogenesis is a multistage process (6).]

In general, later age at start of exposure decreases the relative risk of cancer only when an early stage of carcinogenesis is affected, provided the total extent of exposure is fixed. When a late stage is affected the risk decreases after exposure cessation (5). It is often difficult to distinguish between different models representing early *versus* late stage carcinogenesis from epidemiological data, especially when study populations are not large, because age at start does not vary when duration, age at diagnosis, and time since stopping are fixed. Nevertheless, review of time-related factors in the data set available to us may provide new clues to bladder cancer etiology.

Inferences about tobacco-related bladder carcinogenesis may also emerge from comparing the effects of different types of tobacco. Earlier analyses of the study reported here suggested that black tobacco smoke is 2 to 3 times more carcinogenic than blond tobacco (7). Aromatic amines, including 4-aminobiphenyl and 2-naphthylamine, are more concentrated in black than blond tobacco smoke (8). In addition, a study in the same population showed higher levels of 4-aminobiphenyl hemoglobin adducts in the blood of black tobacco smokers as compared to smokers of blond tobacco.[3] Both 4-aminobiphenyl and 2-naphthylamine are potent human bladder carcinogens in the occupational setting (9); they are also mutagenic (9) and reactive, forming covalent binding with macromolecules (10). Whether the two types of tobacco share a common mechanism of action is unknown. We have previously noted some of the temporal relationships in these data in a preliminary analysis not separated by type of tobacco (11). Temporal aspects of cigarette-related bladder carcinogenesis in the United States have also recently been reported (12), but only blond tobacco is widely used in the United States. In this paper, we further evaluate mechanisms of action including early stage effects by studying the separate impact of black and blond tobaccos in the temporal patterns of bladder cancer risk.

MATERIALS AND METHODS

This study was conducted in the main hospital of the city of Torino in 1977 to 1983. Bladder cancer cases (incident and prevalent) and a sample of patients hospitalized for other diseases were identified, and 95% of them were interviewed. A detailed description of the study design is reported elsewhere (7, 13). Overall, 512 male cases (302 incident, 210 prevalent), 596 male controls, 55 female cases (26 incident, 29 prevalent), and 202 female controls, all residents of the province of Torino and under age 75, are described in the following analysis.

Smoking information included date started and date of cessation, number of cigarettes smoked, brands of the cigarettes smoked, and use of a filter tip for each time period smoked; the lifetime occupational history was also collected. Cigarette brands were classified according to the type of tobacco (*i.e.*, black, blond, or unknown) (7).

In comparison with previous reports, further quality checks have been performed at the International Agency for Research on Cancer; this led to changes in the histories of cigarette smoking for 11 cases and 16 controls.

The analyses reported here are based on logistic regression models, using the LOGIST procedure of SAS.[4] Each model included 7 age groups (<45 and six 5-yr groups). In addition, we introduced duration and years since cessation of smoking (Model I) or age at start and years since cessation (Model II). The four time variables (*i.e.*, age at start, duration, years since cessation, and age at onset) cannot be introduced in the same model because each is a linear combination of the other three. Too few subjects discontinued smoking and then started again to allow us to discern the separate effects of duration and age started. Therefore, Model I and Model II are expected to yield very similar results; the differences between the two can be ascribed to differences in categorization of the variables duration and age started. Nonsmokers were not included in the logistic analyses; the base-line category is represented by the lowest category of each variable in the model.

All analyses were repeated separately for all smokers, black tobacco smokers, and blond tobacco smokers. Black tobacco smokers were defined as those who smoked black tobacco for most of their smoking

Received 7/20/87; revised 3/4/88; accepted 3/28/88.

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[1] This investigation was made possible by a grant to P. V. as Exchange Scientist under the U.S.-Italy Cancer Program, and by a fellowship from the Associazione Italiana per la Ricerca sul Cancro.

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[4] Harrell, unpublished manuscript.

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Table 1 *Number of cases and controls and odds ratios according to duration or age at started smoking, intensity smoked, and number of years since cessation (all male smokers)*

	Cases/controls	Crude OR	OR[a]	95% CI	Trend χ^{2b}
Model I					
Duration					
1–19	24/97	1.0	1.0		4.7
20–39	228/247	3.7	2.6	(1.5–4.5)	($P = 0.03$)
40+	237/153	6.3	3.6	(1.8–7.1)	
Intensity					
1–14	159/220	1.0	1.0		
15–29	276/242	1.6	1.2	(0.9–1.6)	
30+	54/35	2.1	1.8	(1.1–3.0)	
Cessation					
Current	386/314	1.0	1.0		
<3 yr	20/39	0.42	0.35	(0.19–0.64)	
3–9 yr	34/66	0.42	0.43	(0.27–0.70)	0.06
10+ yr	49/78	0.51	0.62	(0.38–1.0)	($P = 0.81$)
χ^2 for model 104.08 (13 d.f.)					
Model II					
Age at start					
25+	18/38	1.0	1.0		
21–24	34/37	1.9	2.0	(1.2–4.2)	4.7
17–20	200/199	2.1	2.2	(1.2–4.1)	($P = 0.03$)
<17	237/223	2.2	2.25	(1.0–4.3)	
Intensity					
1–14	159/220	1.0	1.0		
15–29	276/242	1.6	1.3	(1.0–1.8)	
30+	54/35	2.1	2.0	(1.2–3.3)	
Cessation					
Current	386/314	1.0	1.0		
<3 yr	20/39	0.42	0.33	(0.18–0.60)	11.4
3–9 yr	34/66	0.42	0.39	(0.24–0.62)	($P = 0.0007$)
10+ yr	49/78	0.51	0.40	(0.26–0.60)	
χ^2 for model 92.61 (14 d.f.)					

[a] Logistic regression estimates; models including age at diagnosis/interview.
[b] Based on logistic regression models with variables in a continuous form.

lives (more than 50%). Among males, 87 cases and 109 controls smoked only black tobacco throughout life, whereas 68 cases and 42 controls smoked only black tobacco for most of their lives, but also smoked blond tobacco. Blond tobacco smokers were defined as those who smoked only blond cigarettes for more than 50% of their smoking lives. Of these, 14 of 27 cases and 62 of 76 controls smoked only blond cigarettes throughout life. One hundred cases and 116 controls were mixed smokers for most of their lives (*i.e.*, they smoked both black and blond cigarettes during the same time periods), or switched from black to blond at approximately the midpoint of their smoking life. Overall, 181 cases and 172 controls switched from black to blond tobacco. Intensity of smoking was defined as the number of cigarettes smoked at the midpoint of smoking life. Among females, only 2 cases and 5 controls smoked black tobacco throughout life. Preliminary analyses indicated no appreciable differences between incident and prevalent cases with respect to smoking variables, so all cases were included in the present analysis. Occupational exposures did not exert a confounding effect on the estimates of smoking-related variables.

RESULTS

Table 1 shows the relationship between duration or age at start, intensity, years since quitting, and risks of bladder cancer among all male smokers (all tables, except Table 5, refer to males). It is evident that quitting was followed by a reduction in risk of about 50% within 3 yr. After an immediate drop there was no further lowering in risk with increasing time. Increasing duration or, equivalently, decreasing age at start was associated with an increase in risk. Very few people discontinued smoking and started again. This implied that it was statistically equivalent to estimate the effect of age at starting or duration, when these variables were treated as continuous, and age at diagnosis and time since quitting were included in the model. Thus the χ^2 statistic was the same for age at start and duration. Estimates for categories of duration and age at start are also given. Men who had smoked 40 or more yr showed a risk 3.6 times as high as those who had smoked for less than 20 yr, when intensity of smoking and time since quitting were held constant. Equivalently, men who had begun smoking before the age of 17 had 2.25 times the risk of those who had started after the age of 24. Duration, or age at start, explained more of the variation in risk than intensity did. When only incident cases were considered, the estimates for age at start in Model II were 2.6 (age at start, <17 yr), 2.7 (17 to 20 yr), and 1.6 (21 to 24 yr).

Table 2 reports Model I and Model II for black tobacco smokers, while Table 3 provides the corresponding information for blond tobacco smokers. The trend in relative risk by years since quitting was similar among the two groups of smokers. Compared to men who never smoked, former smokers of black tobacco had an estimated relative risk of 2.1 (1.1 to 4.0), and former smokers of blond had a risk of 1.2 (0.4 to 2.9). Increasing duration was associated with increasing risk in both black and blond tobacco smokers. Among black tobacco smokers, a large difference in risk was shown between the base-line category of age at start (25+ yr) and those less than 25 yr (OR = 2.5). The association between risk and age at start in this group of smokers was similar for different age-at-diagnosis groups. Considering only incident cases, the estimates for age at start were 2.5 (<17 yr), 2.2 (17 to 20 yr), and 1.4 (21 to 24 yr).

Since 181 cases and 172 controls switched from black to blond tobacco, we examined whether switching was associated with decreased risk (Table 4). Within each duration category, switching had no apparent protective effect in comparison with continuing to smoke black tobacco. No subjects in the data set switched from blond to black tobacco.

The effect of smoking filter cigarettes was not consistent. Among black tobacco smokers, those who mostly used filters showed a higher risk than those who mostly used nonfilter cigarettes (OR[5] = 1.4; 95% CI, 0.85 to 2.4), but among blond

[5] The abbreviations used are: OR, odds ratio; CI, confidence interval.

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Table 2 *As in Table 1, male smokers of black tobacco*

	Cases/controls	OR[a]	95% CI	Trend χ^{2b}
Model I				
Duration				
1–19	6/29	1.0		
20–39	68/77	3.4	(1.1–10.0)	2.9
40+	81/45	6.7	(1.7–26.1)	($P \simeq 0.08$)
Intensity				
1/14	50/77	1.0		
15–29	93/62	1.8	(1.1–3.0)	
30+	12/12	1.6	(0.6–4.0)	
Cessation				
Current	115/72	1.0		0.03
<3 yr	10/15	0.46	(0.19–1.15)	($P = 0.87$)
3–9 yr	11/25	0.32	(0.14–0.75)	
10+ yr	19/39	0.59	(0.25–1.38)	
Model χ^2 50.36 (13 d.f.)				
Model II				
Age at start				
25+	6/16	1.0		2.9
21–24	16/15	2.4	(0.7–8.7)	($P = 0.08$)
17–20	63/63	2.3	(0.8–6.9)	
<17	70/57	2.8	(0.9–8.3)	
Intensity				
<15	50/77	1.0		
15–29	93/62	1.9	(1.1–3.3)	
30+	12/12	1.5	(0.6–4.0)	
Cessation				
Current	115/72	1.0		
<3	10/15	0.45	(0.18–1.11)	8.9
3–9	11/25	0.27	(0.11–0.61)	($P \simeq 0.003$)
10+	19/39	0.27	(0.14–0.53)	
Model $\chi^2 = 45.86$ (14 d.f.)				

[a] Logistic regression estimates; models including age at diagnosis/interview.
[b] Based on logistic regression models with variables in a continuous form.

Table 3 *As in Table 1, male blond tobacco smokers*

	Cases/controls	OR[a]	95% CI
Model I			
Duration			
1–19	6/38	1.0	
20–39	10/27	1.1	(0.3–4.7)
40+	11/11	2.5	(0.4–15.7)
Cessation			
Current	20/50	1.0	
1+ yr	7/26	0.54	(0.14–2.08)
χ^2 for model 21.77 (9 d.f.)			
Model II			
Age at start			
17+	19/45	1.0	
<17	8/31	0.8	(0.3–2.4)
Cessation			
Current	20/50	1.0	
1+ yr	7/26	0.36	(0.10–1.23)
χ^2 for model 19.71 (8 d.f.)			

[a] Logistic regression estimates; models including age at diagnosis/interview. Intensity was excluded because of too small variability.

tobacco smokers a lower relative risk was suggested (OR = 0.48; 95% CI, 0.15 to 1.6; estimates adjusted for age at diagnosis, age at start, cessation of smoking). Neither estimate was statistically significant.

Table 5 reports the relative risks for several smoking variables among women. Although numbers of subjects are small, the pattern resembles that observed for male smokers of blond tobacco.

DISCUSSION

In 1972, Doll *et al.* (14) suggested that the concentration of naphthylamine in tobacco smoke (from blond British cigarettes) was comparable to concentrations found in coal-carbonizing plants where an excess of bladder cancer was identified. Black tobacco smoke contains higher concentrations of aromatic amines than blond tobacco (8), and it has been associated with a greater urinary mutagenicity than blond tobacco, both in a study from Germany based on only one black tobacco smoker (15), and in a pilot study from Torino.[6] Thus, the greater risk of bladder cancer that was observed among smokers of black tobacco is compatible with black tobacco's aromatic amine content.

Table 4 *Odds ratios and 95% confidence intervals according to duration and cessation among smokers of black tobacco throughout life and among smokers ... ...switching from black to blond tobacco, males*

All odds ratios are age adjusted; reference category, nonsmokers.

	Black tobacco throughout life		Black tobacco switching to blond[a]	
Duration	Current	Former	Former black current blond	Formerly black, later blond, then quitting
1–19	2.1 (0.2–22.9)[b]	0.8 (0.2–3.0)	3.3 (1.0–10.3)	1.3 (0.1–12.6)
20+	6.6 (3.5–12.6)	2.2 (1.0–4.9)	5.7 (3.3–10.0)	2.6 (1.2–5.6)
All durations	6.2 (3.3–11.7)	2.1 (1.1–4.0)	5.5 (3.2–9.5)	2.5 (1.3–5.0)
Cases/controls	65/47	22/62	151/127	30/45

[a] Including 68 cases and 42 controls smoking mostly black, 13 and 14 smoking mostly blond tobacco, and 100 and 116 mostly mixed smokers.
[b] Numbers in parentheses, CI.

Table 5 *Number of cases and controls and odds ratios according to age started smoking, cessation, and proportion of filtered cigarettes, female smokers*

Values are logistic regression estimates, model including age at diagnosis/interview.

	Cases/controls	OR	95% CI
Age at start			
17+	21/52	1.0	
<17	2/15	0.75	(0.1–5.4)
Cessation			
Current	20/56	1.0	
1+ yr	3/11	0.17	(0.01–1.0)
Filter			
≤50% filtered cigarettes	3/4	1.0	
>50% filtered cigarettes	21/63	0.50	(0.06–4.1)
χ^2 for model 34.07 (9 d.f.)			

One specific aromatic amine, 2-amino-7-naphthol (a metabolite of 2-naphthylamine), was found to be responsible for the highly mutagenic activity of the urine of a smoker (16). In a study in Torino, adducts between various aromatic amines and hemoglobin were sought in the blood of 25 nonsmokers, 43 blond, and 18 black tobacco smokers.[3] Of the 15 aromatic amines studied, only 4-aminobiphenyl showed a positive association with black tobacco. The average concentration of the hemoglobin adduct to 4-aminobiphenyl was 288.3 pg/g in black tobacco smokers, 175,5 in blond tobacco smokers, and 50.8 in nonsmokers. The level among blond tobacco smokers resembled that found in an American population of smokers (17), and studies conducted in the United States reported relative risks for bladder cancer of the same magnitude as those reported among blond tobacco smokers in Torino (12).

The different composition of black and blond tobacco smoke suggests the possibility that various stages of action in a multistage carcinogenic process may be differently affected by the two types of tobacco. Our data from smokers of black tobacco show a greater effect of duration/age at starting to smoke, a lesser effect of intensity, a rapid change in risk after quitting with a plateau well above the level of risk of nonsmokers, and no protection with use of filters. Black tobacco smoke thus appears to contain both early stage and later-stage carcinogens.

[6] Malaveille *et al.*, manuscript submitted for publication.

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Our data from smokers of blond tobacco more closely follow patterns reported from the United States, where blond tobacco is used. For smokers of blond tobacco, the risks following cessation clearly suggested the presence of late-stage carcinogens but did not clearly suggest early stage carcinogens. Use of filters appeared to reduce risk among smokers of blond tobacco, perhaps because filters block the "tar" fraction of smoke, which contains promoters, but not the highly volatile aromatic amines, possible initiators. This finding is consistent with the very high levels of the hemoglobin adduct to 4-aminobiphenyl (>600 pg/g) detected in two smokers of black filtered cigarettes.[3] A relation between filters and late-stage carcinogens would also explain the finding in United States data of a reduction in risk with use of filters among current but not former smokers.

A promoting effect of blond tobacco is also suggested by our data on switching from black to blond tobacco; males who switched showed no drop in risk, whereas those who quit entirely showed a dramatic drop in risk.

Among smokers who used both types simultaneously, a logistic model including age at start, intensity of black or blond tobacco smoking, and cessation of black or blond tobacco smoking gave an odds ratio of 2.5 (95% CI = 1.5 to 4.0) for starting black tobacco before age 25 *versus* starting later. It is interesting that women experienced a pattern of risk for age at start and use of filters, resembling that of male smokers of blond tobacco (Table 5). Nearly all the women smokers in our study exclusively used blond cigarettes.

An early stage effect of smoking black tobacco is consistent with certain properties of aromatic amines, such as mutagenicity and formation of adducts with macromolecules. Furthermore, a few studies of workers exposed to aromatic amines suggest a relationship between temporal variables and bladder cancer risk consistent with an early stage action. In studies by Cartwright (18) on textile workers exposed to dyes and by Decarli *et al.* (19) on workers exposed to 2-naphthylamine, increasing age at first exposure was clearly associated with a decreasing trend in the relative risk. In our study, 42 cases and 22 controls were employed in the dye or the rubber industry; odds ratios decreased by increasing age at first job exposure, but remained stable or actually increased in the years after cessation of work, suggesting an early stage action for occupational exposure to aromatic amines (7). This observation, however, was based on small numbers.

In summary, epidemiological evidence seems to indicate that tobacco smoke contains chemicals having both an early and a late stage effect in bladder carcinogenesis. Biochemical evidence suggests that aromatic amines act as carcinogens in tobacco smoke.

ACKNOWLEDGMENTS

We are grateful to Jay Lubin, Shelia Hoar Zahm, Charles Brown, Richard Hayes, William Blot, and J. F Fraumeni, Jr., for advice and comments, and to Susan Privot and LaShonnah Tyson for technical assistance in the manuscript preparation.

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